BANTAO Journal 2018; 16(2): 96-101

BJ

BANTAO Journal

Original Article

Determining the Risk Factors for Acute Rejection and Glomerular Filtration Rate after Kidney Transplantation

Payam Amini[1], Abbas Moghimbeigi[2], Farid Zayeri[3], Hossein Mahjub[4], Hojjat Sayyadi[5], Mohsen Mohammadrahimi[6] and Saman Maroufizadeh[7]

[1]Department of Biostatistics & Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran; [2]Modeling of noncomunicable Disease Research Center, Department of Biostatistics, Faculty of public health, Hamadan University of Medical Sciences, Hamadan, Iran; [3]Department of Biostatistics, Member of Proteomics Research Center, School of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran;. [4]Research Center for Health Sciences, Department of Biostatistics, Faculty of public health, Hamadan University of Medical Sciences, Hamadan, Iran; [5]Department of Biostatistics and Epidemiology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran; [6]Department of Kidney Transplantation, University of Medical Sciences, Tabriz, Iran; [7]Department of Epidemiology and Reproductive Health, Reproductive Epidemiology Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran

Abstract

Introduction. Several factors cause low estimated glomerular filtration rate (eGFR) as well as acute rejection after kidney transplant. This study aims to determine risk factors affecting low eGFR as well as the frequency of acute rejections during one year after kidney transplantation recruiting a longitudinal joint modeling approach.
Methods. Using the information from 129 kidney transplant patients, the eGFR and the frequency of acute rejections were recorded for three time points of 4, 8 and 12 months after kidney transplant. Using a longitudinal joint model, the adjusted effects of predictors were assessed on both the eGFR and the frequency of acute rejections, jointly.
Results. The results demonstrated that being one year younger reduces the risk of higher stages of eGFR (OR=1.053, p<0.001). Males were more prone to experience lower stages of the eGFR (OR=3.571, p<0.001). Patients with chronic allograft necrosis were at risk of higher stages of the eGFR (OR=3.048, p=0.001). The frequency of acute kidney transplant rejections for a patient without anti-thymocyte globulin is 6.398 times higher than with anti-thymocyte globulin (p=0.048). The absence of urinary tract infection was the only factor leading to zero rejections. Acute rejection was more potential for a BIL-D liver dysfunction patient with a factor of 2.487 in comparison to BIL-T.
Conclusions. Our study revealed that the absence of urinary tract infection strongly results in zero rejections. Factors such as chronic allograft necrosis cause lower eGFR score. The frequency of rejections is affected by anti-thymocyte globulin, BIL-T liver dysfunction.

Keywords: kidney transplantation, transplant rejections, glomerular filtration rate, longitudinal study

Introduction

Chronic Kidney Disease (CKD) is a global public health problem [1]. The increasing prevalence and incidence of CKD may result in complications in kidney function and cardiovascular disease [1]. It is well known that CKD can be a very important candidate for development of cardiovascular disease and end-stage renal disease [2,3]. Chronic renal failure is defined as less than 60 ml/min estimated glomerular filtration rate (eGFR) for more than three months [4]. The prevalence of CKD varies across different regions such as 10.8% in China in 2012, 11.2% in Australia in 2006 and 10 to 15% in united states of America in 2009 [5-7]. Moreover, chronic kidney dysfunction and recurrence of glomerulonephritis can be the main reasons for long-term graft loss [8]. Many factors such as leukopenia and human leukocyte antigen (HLA) type, type of donor (e.g., living or cadaver) and donor's age and race, recipient's serum creatinine level, sex, age and health status may cause a chronic loss of graft. Reaching end-stage chronic kidney disease is the main reason for kidney transplant in which the eGFR is less than 15 ml/min [4]. It is argued that the prevalence of end-stage renal disease in Iran is high [9]. According to the reports more than 2000 kid-

Correspondence to: Abbas Moghimbeigi, Associate Professor, Modelling of noncomunicable Disease Research Center, Department of Biostatistics, faculty of public health, Hamadan University of Medical Sciences, Hamadan, Iran. ORCID: 0000-0002-3803-3663, P.O. Box: 6517838736; Phone: +98-9125683772, Email: moghimb@gmail.com

ney transplants were performed in 2012 in Iran [10]. Kidney transplant has been introduced as one of the most efficient treatments for patients who suffer from CKD in the end-stage. However, not all of the transplants are successful. Depending on the immunosuppressive strategies, 10-15% of patients in the first year experience an acute rejection [11]. In spite of the morbidity of patients, immunosuppressive therapy has been advanced and has resulted in decrease of acute rejection [12]. During the first 10 years, an approximation of 40% of renal allografts fail. Moreover, the number of transplants decrease annually [13]. Assessing and observing the changes in eGFR is necessary for the care of renal transplant recipients. The progression of kidney disease can be predicted by eGFR. In the early stages after transplantation, several important clinical factors may influence kidney graft function such as blood residues, rejection episodes, and acute immunosuppressive drug toxicity. Hence, after transplantation, the number of acute kidney transplant rejections may be associated to the eGFR [14].

Count and ordinal data are recorded in a multitude of settings. Using the GLMMs, variety of models can be performed based on the distribution of the response variable. For a count data, a Poisson distribution with a log-linear link function is commonly assumed, while the mean and variance of count response are equal. In the case of inequality due to the extra heterogeneity, overdispersion would be considered in the modeling process. Negative binomial is a common choice to address this issue. In the case of inflated zeros in the data, zero-inflated models are performed [15]. Ordinal data is a special form of categorical data while the order of the response categories is of importance. Analyzing methods for binary data has been extended to nominal and ordinal categorical outcomes [16]. Longitudinal joint models have been applied extensively in medical area. Some studies have used longitudinal joint modeling to model serial echocardiographic measurements of aortic gradient, aortic regurgitation and measurements of the occurrence of death jointly [17], to investigate the joint evolution of longitudinal pulse and respiratory rate of congestive heart failure patients [18], to assess the hemodynamic effect on diastolic blood pressure, systolic blood pressure and heart rate over time [19], to evaluate the development of longitudinal occurrence and prevalence of antimicrobial resistant zoonotic agents [20], and to investigate the children body weight and number of days of diarrhoeal illness recorded at 7 time-points of follow-up [21].

The main objective of this study is to evaluate the joint evolution of acute kidney transplant rejection and eGFR of patients after one year of kidney transplantation. Besides, identifying the potential risk factors for the two longitudinal outcomes is carried out through the joint model.

Materials and methods

Participants and study design

A total of 129 patients records were checked and used in this historical cohort study. The patients referred to the kidney transplant center of the Imam Khomeini Hospital of Urmia University of Medical Sciences from 2003 to 2014. More details about the inclusion and exclusion criteria, sample size, the study protocol and ethical considerations are well explained by Sayyadi *et al*. [22].

In the current study, two main longitudinal response variables, acute kidney transplant rejection as the count variable and estimated glomerular filtration rate as an ordinal variable in 5 states were assessed. These variables were recorded every 4 month after the transplantation for one year. Glomerular filtration rate was estimated from abbreviated prediction equation provided by the Modification of Diet in Renal Disease study (MDRD). The estimated glomerular filtration rate among an Iranian population is calculated as follows:

The stages were determined using the National Kidney Foundation (NKF) criteria as stage 1 with normal or high eGFR (eGFR > 90 mL/min), stage 2 Mild chronic kidney disease (eGFR=60-89 mL/min), stage 3 Moderate chronic kidney disease (eGFR=30-59 mL/min), stage 4 Severe chronic kidney disease (eGFR=15-29 mL/min) and stage 5 end stage chronic kidney disease (eGFR <15 mL/min) [1].

The independent and predictor variables were the type of kidney donor (relative/ non-relative), recipient's age and sex, anemia (yes/no), type of medication (Azathioprine/ Cellcept/both/none), diabetes (yes/no), and anti-thymocyte globulin (yes/no), as well as complications after transplantation, such as proteinuria (yes/no), hyperkalemia (yes/no), hyperuricemia (yes/no), leukopenia (yes/no), myocardial infarction(yes/no), delayed graft function (yes/no), acute tubular necrosis (yes/no), urinary tract infection (yes/no), chronic allograft necrosis (yes/no), dyslipidemia (TG/ CHOL), liver dysfunction (BIL-T/ BIL-D), and hypercalcemia (yes/no).

Statistical analysis

The descriptive statistics of the patients are shown as frequency (percentage). Repeated measures over time and across several cases causes a special kind of variance which must be analyzed through longitudinal analysis methods. Among different kinds of models, Generalized Linear Mixed effects Models (GLMMs) deal with the intra-class correlation caused by longitudinal repeated measures using random effects in the model. These approaches provide subject specific interpretation as well as population average [23]. In the present study, random intercepts in the models were used to consider the correlation between repeated measures for the same patient.

Separate modeling of associated response variables provide less accurate estimations. Joint modeling approaches

increase the accuracy of estimations by reducing their standard errors [15].

Let y_{1ij} and y_{2ij} represent the frequency of acute rejections and eGFR respectively, for subject *i* at the occasion j. In the following models, x_{ij} and z_{ij} are the covariates, β and α are the coefficients, θ_c is the estimated threshold of the c^{th} category of eGFR, w_i and b_i are the random effects. The random intercepts are correlated through the correlation parameter ρ and hence the association between eGFR and frequency of acute rejections are considered. The two associated response variables follow the general form as follows:

$$E(y_{1ij}) = e^{x_{ij}\beta + w_i}$$

$$pr(Y_{2ij} \leq c) = \frac{e^{b_i + \theta_c - z_{ij}\alpha}}{1 + e^{b_i + \theta_c - z_{ij}\alpha}}$$

In the case of inflated zeros in the frequency of acute rejections, zero-inflation models are used such as zero-inflated Poisson (ZIP). To check the zero inflation, Vuong test is used.

Results

A total number of 129 patients were followed for one year after kidney transplantation; their rejection status as well as eGFR were recorded on months 4, 8 and 12. The hospital records from September 2003 to December 2014 were checked. About 63% of patients were male (79 patients), 72% with hypertension, 10.9% relative donors, 3.1% with delayed graft function (DGF), 5.4% with acute tubular necrosis (ATN), 2.4% with myocardial infarction, 54.8% with urinary tract infection (UTI), 68.2% with chronic allograft necrosis (CAN), 61.9% with Hyperuricemia, 19.4% with anti-thymocyte globulin (ATG), 65.1% with Proteinuria, 6.2% with Hyperkalemia, 39.5% with liver dysfunction, 82.2% with dyslipidemia, 17.1% with Hypercalcemia, 48.8% with anemia and 21.75 with diabetes. The distribution of two response variables, eGFR and number of acute rejection of kidney transplantation during months 4, 8 and 12 is illustrated in Table 1. No significant difference was detected longitudinally.

Table 1. The frequency (percentage) of eGFR stages and acute rejections at months 4, 8 and 12 among 129 patients

Response variables	Stage	time 4	8	12	p-value
Estimated glomerular filtration rate	1	25(19.4)	37(28.7)	26(20.2)	0.697
	2	55(42.6)	50(38.8)	55(42.6)	
	3	35(27.1)	32(24.8)	36(27.9)	
	4	6(4.7)	4(3.1)	4(3.1)	
	5	8(6.2)	6(4.7)	8(6.2)	
acute kidney transplant rejection	0	112(86.8)	111(86)	115(89.1)	0.966
	1	10 (7.8)	10(7.8)	8(6.2)	
	2	3(2.3)	4(3.1)	2(1.6)	
	3	1(0.8)	3(2.3)	2(1.6)	
	4	1(0.8)	0(0)	1(0.8)	
	5	2(1.6)	1(0.8)	1(0.8)	

The results from longitudinal joint model of eGFR and acute rejection of kidney transplantation are shown in Table 2. The simple GLMM was separately used to find the potential factors for the joint model. To do so, variables with p-value <0.15 were included in the joint model. Moreover, the Vuong test was applied (z-value =3.35, p-value=0.0004) and the application of ZIP model for the eGFR was confirmed. According to the outputs, the odds ratio of being in a lower stage of eGFR for one year older patient is 0.949. It means that being one year younger increases the odds of being in a lower stage of eGFR with the odds ratio of 1.053 (p<0.001). Females were less prone to experience a lower stage of eGFR compared to males. Being in lower stage of eGFR for females was 0.280 times more than men. In other words, men were 3.571 times more likely to experience lower stages of eGFR (p<0.001). Patients without chronic allograft necrosis experienced lower stages of eGFR with the odds ratio of 0.328. That is so those with chronic allograft necrosis were 3.048 times more likely to be in the lower stages of eGFR (p=0.001). The results exposes that time, DGF, ATN and being diabetic did not affect eGFR. The acute rejection of kidney transplantation was assessed by ATG, DGF, UTI, CAN, liver dysfunction and time. The expected number of rejections for a patient without ATG is 6.398 times the expected number of rejections for a patient with ATG (p=0.048). In patients without UTI, the expected number of rejections would decrease by a factor of 0.443. Moreover, rejection was more potential for a BIL-D liver dysfunction patient with a factor of 2.487 in comparison to BIL-T. UTI was the only factor caused zero rejections significantly. The odds of zero rejections for patients without UTI was 0.358 times than those with UTI. In other words, patients with UTI are luckier to experience rejections with the odds ratio of 2.793 (p=0.049). Although the correlation between the random intercepts was not significant (correlation=0.252, p=0.671), a positive correlation between eGFR stages and the frequency of acute kidney transplant rejection was observed.

Table 2. The results of longitudinal joint modeling of eGFR and acute kidney transplant rejection

Response	Parameter	Estimate	SE*	p-value	95% CI†		OR‡
Estimated glomerular filtration rate	Age	0.052	0.011	<0.001	0.028	0.075	1.053
	Sex (female)	1.272	0.338	<0.001	0.603	1.941	3.568
	Diabetes (No)	0.238	0.362	0.511	-0.955	0.478	1.269
	ATN§ (No)	-0.372	0.631	0.555	-0.874	1.618	0.689
	DGF‖ (No)	-2.162	0.157	0.063	-0.127	4.452	0.115
	CAN¶ (No)	1.114	0.341	0.001	-1.791	-0.438	3.047
	Time (month)	-0.005	0.030	0.851	-0.066	0.054	0.995
	Standard deviation of the random intercept	0.451	0.071	<0.001	0.309	0.593	-
Acute kidney transplant rejection	ATG# (NO)	1.856	0.931	0.048	0.012	3.699	6.398
	DGF (NO)	-1.290	1.684	0.445	-4.623	2.043	0.275
	UTI** (NO)	-0.815	0.390	0.038	-1.587	-0.043	0.443
	CAN (NO)	0.385	0.357	0.283	-0.322	1.093	1.470
	Liver Dysfunction	0.911	0.404	0.026	0.111	1.712	2.487
	Time (month)	-0.054	0.051	0.291	-0.156	0.047	0.947
	Standard deviation of the random intercept	0.440	0.275	0.112	-0.104	0.985	-
Zero Inflation	ATG (NO)	1.184	1.576	0.453	-1.934	4.303	3.267
	DGF (NO)	-1.341	1.552	0.389	-4.413	1.730	0.262
	UTI (NO)	-1.026	0.518	0.049	-2.051	-0.001	0.358
	CAN (NO)	0.579	0.463	0.199	-0.319	1.514	1.784
	Liver Dysfunction	0.645	0.556	0.248	-0.455	1.746	1.906
	Time (month)	-0.021	0.070	0.761	-0.161	0.118	0.979
Correlation between the random intercepts		0.252	0.593	0.671	-0.921	1.425	-

* Standard Error; † 95% Confidence Interval; ‡ Odds Ratio; § acute tubular necrosis; ‖ delayed graft function; ¶ chronic allograft necrosis; # anti-thymocyte globulin, ** urinary tract infection

Discussion

In the current study, longitudinal data of patients with kidney transplants were utilized to find significant factors of eGFR and the frequency of acute kidney transplant rejection by recruiting longitudinal joint modeling approach. The distribution of patients across five stages of eGFR did not differ during three time points (one year) as well as the frequency of acute kidney transplant rejection. At the end of the first, second, third and four months the majority of patients were observed in stage two of eGFR. However, a slight difference was shown between month eight in comparison to months four and 12. In other words, except for the stage four, the distribution of eGFR is almost the same for months four and 12. The frequency of acute kidney transplant rejection was the same longitudinally during one year and the majority of patients had no rejections.

The results from longitudinal joint model showed that older patients and females are more likely to experience higher stages of eGFR. O'Hare *et al*. assessed the influence of age among chronic kidney patients using a large number of cases followed for more than three years. They showed that age strongly affects patients with eGFR more than 60 ml/min per 1.73 m^2 resulting in a higher rate of death among older patients [24]. Stevens *et al*. evaluated the performance of the CKD epidemiology collaboration in renal disease study equations to estimate GFR levels above 60 ml/min/1.73 m^2 and revealed that participants with higher eGFR were younger [25]. In another study, Hallan *et al*. exposed the association of kidney measures with mortality and end-stage renal disease regarding age. Considering age as a factor, they aimed to investigate the association of eGFR and albuminuria with clinical risks. They showed that mortality risk for reduced eGFR decreased with increasing age [26]. Our study assessed the adjusted effects of age and sex beside to several factors in a joint model with multiple effects. Although the main determining factor of eGFR is creatinine which remains constant daily, it is a function of creatinine, sex and age. Therefore, a reverse association between eGFR and female gender and older age is expected [27,28].

The results showed that DGF, ATN and being diabetic did not affect eGFR. Hollmen *et al*. evaluated whether donor neutrophil gelatinase-associated lipocalin could be a predictor of DGF after transplantation. Applying a multivariate analysis, they introduced eGFR as a risk factor for prolonged DGF [29]. Esson and Schrier discussed the diagnosis and treatment of acute tubular necrosis which is associated with decrease in glomerular filtration rate [30].

It is well known that ATG prevents acute rejection in organ transplantation [27,28]. It is argued that, patient

without ATG experienced more rejections. In a study by Brennan *et al*. ATG was compared with Basiliximab in rabbits with renal transplantation and they demonstrated that the ATG group had lower incidences of acute rejection [31].

The frequency of rejections was more potential for a BIL-D liver dysfunction patient. Those cases without an experience of UTI had less number of rejections and using the zero-inflated model, UTI was the only factor resulting in zero rejections. Parikh et al. conducted a retrospective review to evaluate the urinary tract infections after renal transplantation. They concluded that UTI can increase mortality risk in renal transplant recipients. The authors showed that although chronic immunosuppressive medications are necessary for patients after kidney transplantation, this may increase infections rates such as UTI [32]. Kidney transplantation is followed by some adverse outcomes such as bleeding, acute rejections and infections. Taking immunosuppressant drugs increases the risk of infections after transplantation and this might lead to rejections. Hence, there is a negative association between infections and acute rejection [27,28].

Longitudinally recording of the data benefits the researchers to investigate the development of response variables over the time and provides a significant more amount of information about medical and clinical problems in contrast to cross sectional type of studies [15, 23]. Generalized linear mixed-effects models are frequently used to analyze longitudinal data. Joint modeling approaches take the natural associations among response variables into account which is ignored by univariate approaches. This procedure causes a smaller standard errors for estimated coefficients resulting in a true significance of effects [15,33]. Evaluating several response variables, Fieus *et al*. applied a joint random effects model approach to assess the development of responses jointly, over the time [34]. Analyzing Lin *et al*. used GLMMs to model clustered continuous and binary response variables jointly to analyze the development of ethylene glycol in mice [35]. Azen and Budescu suggested utilizing joint approaches in order to consider the association of response variables [36]. Badiru compared computational survey of the various univariate and multivariate learning curve models showed that the bivariate model provides a slightly better fit than the univariate model. Moreover, the bivariate model provided more detailed information about the data [37]. Thorp used longitudinal joint and univariate mixed-effects models for metabolic syndrome data in which multiple outcome variables were assessed using several predictors. He found that the multivariate model is able to deal with the same questions addressed as the univariate model. Joint models answer additional important questions about the association in the evolutions of the response variables as well as the evolution of the associations. He showed that taking the association between the responses reduces the standard errors in estimations and leads to more reliable results [38].

The limitations of our study were the inaccessibility to the cases to reach a relative large sample size and also to follow the cases for over one year after transplantation. Moreover, the side effects of the drugs have not been assessed. However, the data was collected in one of the most referral centers and a powerful statistical approach was used to analyze the data.

The present study showed that after adjusting the association between acute kidney transplant rejection and eGFR, females, older patients and those with chronic allograft necrosis were more likely to experience lower eGFR score. Patient with ATG, BIL-T liver dysfunction and without UTI experienced less number of rejections. UTI was determined as the only significant factors causing zero acute rejections.

Conflict of interest statement. None declared.

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